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Original Scientific Paper

Adverse clinical events in patients treated with sirolimus-eluting stents: the impact of Type D personality

Susanne S. Pedersen^{a,b}, Johan Denollet^b, Andrew T.L. Ong^a,
Karel Sonnenschein^a, Ruud A.M. Erdman^{a,c}, Patrick W. Serruys^a
and Ron T. van Domburg^a

^aDepartment of Cardiology, Thoraxcentre, ^bDepartment of Medical Psychology and Psychotherapy, Erasmus Medical Centre Rotterdam and ^cCoRPS – Centre of Research on Psychology in Somatic diseases, Tilburg University, The Netherlands

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Background Little is known about the impact of psychological risk factors on cardiac prognosis in the drug-eluting stent era. We examined whether the distressed personality (Type D) moderates the effect of percutaneous coronary intervention with sirolimus-eluting stent implantation on adverse clinical events at 2-year follow-up. Type D is an emerging risk factor in patients with cardiovascular disease.

Design Prospective follow-up study.

Methods Three hundred and fifty-eight patients with ischemic heart disease, who consecutively underwent percutaneous coronary intervention with sirolimus-eluting stent as part of the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital registry, completed the Type D Scale (DS14) post-percutaneous coronary intervention (PCI). The end-point was a composite of death and non-fatal myocardial infarction 2 years after PCI.

Results At follow-up, there were 22 events (12 deaths and 11 myocardial infarctions). Type D patients had a greater than two-fold risk of an event at follow-up compared with non-Type D patients (10.4 vs. 4.4%, $P=0.031$). In multivariable analysis, Type D remained an independent predictor of adverse outcome (hazard ratio: 2.61; 95% confidence interval: 1.12–6.09; $P=0.027$) adjusting for sex, age, and history of coronary artery disease, multivessel disease, diabetes, hypercholesterolemia, hypertension, renal impairment and smoking. Previous cardiac history was also an independent predictor of death or myocardial infarction (hazard ratio: 2.83; 95% confidence interval: 1.00–7.96; $P=0.049$).

Conclusions Type D personality moderated the effect of percutaneous coronary intervention on hard clinical events despite treatment with the latest innovation in interventional cardiology. The inclusion of psychological risk factors in general and personality factors in particular may optimize risk stratification in the drug-eluting stent era. *Eur J Cardiovasc Prev Rehabil* 14:135–140 © 2007 The European Society of Cardiology

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Keywords: mortality, myocardial infarction, percutaneous coronary intervention, sirolimus-eluting stents, Type D personality

Introduction

The drug-eluting stent represents a breakthrough in the 25-year history of interventional cardiology. Drug-eluting stent implantation has to a large extent done away with restenosis, the 'Achilles heel' of percutaneous coronary

intervention (PCI) and thereby the need for repeat revascularization [1–3]. In the future, drug-eluting stent implantation is likely to become the treatment of choice. In the US, it has been estimated that 80% of eligible patients would be treated with drug-eluting stents at the end of 2003 [4]. In randomized, controlled trials, drug-eluting stents have not been shown to confer any benefits on the incidence of death or myocardial infarction (MI) [5]. This has also been confirmed in

Correspondence to Dr Susanne S. Pedersen, PhD, CoRPS, Department of Medical Psychology, Room P503a, Tilburg University, Warandelaan 2, P.O. Box 90153, 5000 LE Tilburg, The Netherlands
Tel: +31 13 466 2503; fax: +31 13 466 2067; e-mail: s.s.pedersen@uvt.nl

registries of unselected patients, who represent the 'real world' of interventional cardiology [6].

In the drug-eluting stent era, there is therefore still a need to identify risk factors in order to improve risk stratification in patients treated with this innovative technique. The study of non-traditional risk factors, such as psychosocial factors, in addition to the traditional risk factors may help identify subgroups of patients at risk of adverse prognosis. The inclusion of psychosocial risk factors in research and clinical practice has also been advocated in the recent guidelines of the European Society of Cardiology on the prevention of coronary artery disease (CAD) [7] and elsewhere [8]. Moreover, in the predrug-eluting stent era the majority of studies on the impact of psychosocial factors on cardiac prognosis have been conducted in post-MI patients. Less emphasis has been given post coronary artery bypass graft surgery (CABG) patients [9] and even less focus on post-PCI patients [10].

The distressed personality type (Type D), an emerging risk factor, has been shown to contribute to the pathogenesis of CAD [11–14]. Type D has also been associated with increased distress and impaired health status [15,16]. Type D refers to individuals who tend to experience increased negative emotions and who do not express these emotions in social interactions owing to fear of how others may react [14]. Due to the inclusion of the social inhibition component, Type D is more than just negative affect, such as depression, in that the construct also assesses how patients deal with these negative emotions. It is only patients who score high on both negative affectivity and social inhibition that are at increased risk, with social inhibition modulating the effect of negative emotions on clinical outcome [17]. Studies in the pre drug-eluting stent era have shown that the prognostic value of Type D personality is as powerful as left ventricular dysfunction, and that the impact of Type D on prognosis is independent of disease severity [11–14] and short-term changes in mood, such as depression and anxiety [12,13]. Initial analyses from the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry suggested that Type D personality may be a risk factor for adverse clinical events 15 months post-PCI (i.e. 9 months following assessment of Type D) [18]. Given the relatively short-term follow-up, however, we included patients treated with sirolimus-eluting stent (SES) as well as bare metal stent implantation, and did not examine whether Type D moderates the effect of PCI on prognosis in the drug-eluting stent era, that is in patients treated exclusively with SES [18].

In this study, we therefore investigated whether Type D personality predicts the occurrence of adverse clinical events at 2 years in post-PCI patients treated exclusively with SES.

Methods

Patient population and study design

Unselected consecutive patients with ischemic heart disease undergoing PCI with SES (Cypher; Johnson & Johnson-Cordis unit, Cordis Europa NV, Roden, The Netherlands), who participated in the RESEARCH registry between April and October 2002, qualified for inclusion in the current study. Details of the RESEARCH registry have been published elsewhere [19]. The registry was designed to reflect the 'real world' of interventional cardiology for which reason all patients were eligible for enrolment regardless of anatomical or clinical presentation. In brief, the purpose of the registry was to investigate the impact of SES implantation on the clinical outcomes of patients treated with PCI.

At 6 months, all living patients ($n = 549$) were contacted by letter and asked to fill in a psychological questionnaire (see Materials), of which 358 (65%) returned the questionnaire. All patients were prospectively followed-up for clinical adverse events.

Apart from responders being older than non-responders (62 vs. 60 years; $P < 0.05$), we found no other statistically significant differences between the two groups on demographic and clinical characteristics at the time of administration of the psychological questionnaire.

The registry was approved by the hospital ethics committee, and it was carried out in accordance with the Helsinki Declaration. Every patient provided written informed consent.

Materials

Demographic and clinical variables

Demographic variables included sex and age. Information on clinical variables (MI, previous PCI, previous CABG, multivessel disease, hypertension, hypercholesterolemia, diabetes mellitus, renal impairment, and smoking status) was obtained from the patients' medical records.

Type D personality

Type D personality was assessed with the Type D Scale (DS14), a 14-item scale rated on a 5-point Likert scale from 0 (false) to 4 (true) [20]. The scale consists of two subscales, that is, the stable traits of negative affectivity (e.g. 'I am often in a bad mood') and social inhibition (e.g. 'I am a 'closed' person'). A high score on both components (using a standard cut-off score ≥ 10) denotes those with a Type D personality. Type D defines individuals who tend to experience increased negative emotions and who do not express these emotions in social interactions. The DS14 has adequate reliability with Cronbach's $\alpha = 0.88$ and $\alpha = 0.86$ for the negative affectivity and the social inhibition subscales, respectively [20]. The test-retest reliability $r = 0.72/0.82$ for the negative affectivity

and social inhibition subscales indicates that the two traits reflect stable tendencies to experience negative emotions paired with the tendency not to express these emotions across time and situations [20]. As described elsewhere, the DS14 was administered 6 months post-PCI [18].

Clinical endpoint and definitions

The endpoint was defined as the occurrence of a composite of death (all-cause) or non-fatal MI at 2 years after PCI (i.e. 18 months after assessment of Type D personality). MI was diagnosed by a rise in the creatine kinase-MB level to more than three times the upper normal limit [21]. Deaths ($n = 14$) occurring between the index event and administration of the psychological questionnaire were excluded from statistical analyses. MIs that occurred before the administration of the questionnaire were included as prior MIs in analyses. Reported baseline characteristics are characteristics at the time of administration of the DS14.

Statistical analysis

Discrete variables were compared with the χ^2 test (Fisher's exact test when appropriate) and continuous variables with the Student's *t*-test. The cumulative adverse event rate at 2-year follow-up was calculated according to the Kaplan–Meier method. The log-rank test was used to compare the event rate between Type D and non-Type D patients. Univariable and multivariable Cox proportional hazards regression analyses were performed to investigate the impact of Type D personality on the endpoint at 2-year follow-up. In multivariable analysis, we adjusted for sex, age ≥ 60 history of CAD (defined as MI, PCI, or CABG before the index event), multivessel disease, diabetes, hypercholesterolemia, hypertension, renal impairment, and smoking. All statistical tests were two-tailed. $P < 0.05$ was used for all tests to indicate statistical significance. Hazard ratios (HR) with 95% confidence intervals (CI) are reported. All statistical analyses were performed using SPSS for Windows version 12.0.1 (SPSS Inc., Chicago, Illinois, USA).

Results

Baseline characteristics of patients stratified by personality type are shown in Table 1. Of the 358 patients, 106 (30%) had a Type D personality, which is consistent with the prevalence found in other studies of cardiac patients [11–13]. The only significant difference on baseline characteristics was found on smoking with Type D patients being more likely to smoke than non-Type D patients.

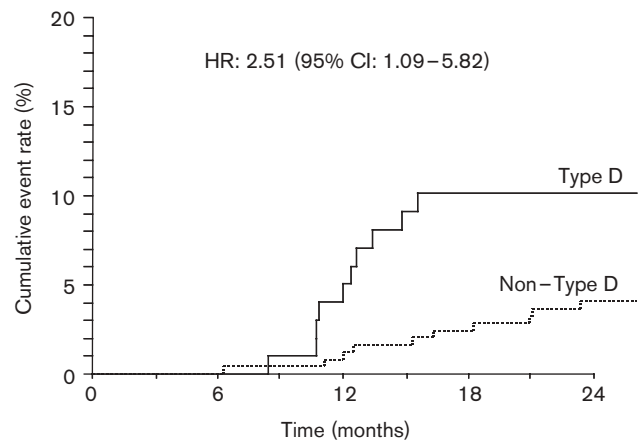
Between baseline and 2 years follow-up (mean = 24 months; median = 25 months), 23 events (12 deaths and 11 MIs) had occurred. One patient had suffered both events reducing the total number of events to 22 for regression analyses.

Table 1 Baseline characteristics (6 months after PCI)

	Type D (<i>n</i> = 106) <i>n</i> (%)	Non-Type D (<i>n</i> = 252) <i>n</i> (%)	<i>P</i>
Demographics			
Female sex	33 (31)	70 (28)	0.522
Age (years) mean (SD)	61 (11)	63 (10)	0.125
Clinical risk factors			
Previous MI ^a	38 (36)	79 (31)	0.392
Previous PCI	32 (30)	73 (29)	0.817
Previous CABG	10 (9)	36 (14)	0.210
Multivessel disease	59 (56)	133 (53)	0.618
Hypertension ^b	44 (42)	105 (42)	0.978
Hypercholesterolemia ^c	84 (79)	199 (79)	0.953
Diabetes mellitus ^b	19 (18)	39 (16)	0.566
Renal impairment ^d	21 (20)	52 (21)	0.865
Smoking ^e	37 (35)	58 (23)	0.020

Previous CABG, coronary artery bypass surgery before index event; previous MI, myocardial infarction before index event; previous PCI, percutaneous coronary intervention before index event. ^aOn the basis of the judgement of the treating physician. ^bPresent if being treated for the condition. ^cTotal cholesterol levels > 240 mg/dl or on lipid-lowering medication. ^dIndicated by creatinine clearance < 61 ml/min. ^eOn the basis of on self-report. * $P < 0.05$.

Fig. 1



Kaplan–Meier curves for 2-year cumulative risk of death or non-fatal myocardial infarction stratified by Type D personality (unadjusted analyses). Time refers to time since sirolimus-eluting stent (SES) implantation. CI, confidence interval; HR, hazard ratio.

At follow-up, patients with a Type D personality had experienced significantly more events than non-Type D patients [11/106 (10.4%) vs. 11/252 (4.4%), $P = 0.031$]; Type D patients had a greater than two-fold (HR: 2.51; 95% CI: 1.09–5.82) risk of death or MI (Fig. 1).

In multivariable analysis, Type D remained an independent predictor of adverse outcome (HR: 2.61; 95% CI: 1.12–6.09), adjusting for sex, age, and clinical risk factors (Table 2). Previous cardiac history was also an independent predictor of death or MI (HR: 2.83; 95% CI: 1.00–7.96) (Table 2).

Discussion

This is the first study to examine whether psychological risk factors in general and Type D personality in particular

Table 2 Predictors of death or MI at 2-year follow-up (adjusted analysis)^a

Predictor variables	HR (95% CI)	P
Type D	2.61 (1.12–6.09)	0.027*
Female sex	0.62 (0.22–1.79)	0.379
Age \geq 60 years	1.12 (0.43–2.94)	0.814
CAD history ^b	2.83 (1.00–7.96)	0.049*
Multi-vessel disease	1.95 (0.74–5.13)	0.179
Diabetes ^c	2.40 (0.92–6.23)	0.072
Hypercholesterolemia ^d	0.94 (0.31–2.84)	0.907
Hypertension ^c	0.88 (0.36–2.15)	0.772
Renal impairment ^e	2.05 (0.77–5.44)	0.150
Smoking ^f	2.07 (0.78–5.46)	0.142

CABG, coronary artery bypass surgery; CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction. ^aEnter procedure.

^bMI, PCI or CABG before the index event. ^cPresent if being treated for the condition. ^dTotal cholesterol levels >240 mg/dl or on lipid-lowering medication.

^eIndicated by creatinine clearance <61 ml/min. ^fOn the basis of self-report. * $P<0.05$.

moderate the effect of PCI on clinical events in patients treated exclusively with drug-eluting stents. In post-PCI patients treated with SES, we found that Type D was associated with a greater than two-fold risk of mortality or non-fatal MI, adjusting all demographic and clinical risk factors. This shows that Type D patients do not benefit from SES implantation on par with non-Type D patients.

The findings of the current study suggest that Type D moderates the effect of PCI with SES on hard clinical events. In the pre drug-eluting stent era, Type D has also been shown to moderate the effects of treatment in patients with established CAD [22], and to be associated with adverse prognosis [11–14]. Similar results were found in a mixed group of patients treated with SES or bare metal stent implantation [18].

Several pathways are present through which Type D personality may exert an adverse impact on prognosis. Type D patients may be less likely to engage in optimal health-related behaviours, such as adhering to dietary restrictions, exercising and quitting smoking. Our data support this notion, as Type D patients were more likely to smoke than non-Type D patients. Nevertheless, the effect of Type D remained when adjusting for smoking in multivariable analysis. Unfortunately, no other health-related behaviours were assessed in the study.

Inflammation may provide another mechanism. Atherosclerosis is increasingly being recognized as an inflammatory process [23], and in turn inflammatory markers such as C-reactive protein [24] and white blood cell count [25] have been associated with an increased risk of mortality post-PCI. Studies indicate that an inflammatory response follows subsequent to stent deployment owing to injury to the vessel wall [26], but also that inflammatory status before PCI may be an important determinant of clinical outcome after PCI [26]. In patients with chronic heart failure, Type D has been associated with increased levels

of TNF- α and TNF- α -soluble receptors 1 and 2 [27], which are important predictors of mortality in chronic heart failure [28]. It is possible that Type D patients differ in their inflammatory status before PCI and their response after PCI compared with non-Type D patients, in turn rendering them at increased risk of adverse clinical outcome.

The findings of the current study have implications for research and clinical practice, and underscore the importance of including psychological risk factors in general and personality factors in particular. This was also advocated in the recent guidelines of the European Society of Cardiology for the prevention of cardiovascular disease [7]. The Type D Scale has been recommended as one of the screening tools to use in clinical practice [8], and the scale is included in the Euro Cardio-QoL Project, which has an objective of developing a core heart disease health-related quality of life questionnaire [29]. The extent to which Type D moderates the effect of cardiac rehabilitation deserves further attention. Although it is speculative, the results of the current study and previous studies showing that Type D moderates the effect of medical treatment [18,22] suggest that Type D patients may also be less likely to benefit from standard cardiac rehabilitation programmes, probably owing to their tendency not to express negative emotions when together with others. These patients may be quieter in a rehabilitation setting and less likely to share information with an emotional content. Hence, Type D patients may need more encouragement to talk about their feelings than non-Type D patients, although a prerequisite for sharing their emotions will be that they experience the rehabilitation context as sufficiently safe and pleasant. Individual therapy sessions may also be helpful for Type D patients, as a one-to-one relationship is less threatening to them than a group setting.

Prospective studies are now warranted that investigate the extent to which Type D also moderates the effect of cardiac rehabilitation on prognosis, and which mechanisms may be responsible for the adverse effect of Type D on cardiac prognosis, be they behavioural, physiological or a combination thereof. Knowledge of these mechanisms is likely to point to targets for intervention, such that Type D patients may benefit from treatment, including cardiac rehabilitation, on par with non-Type D patients and have a better prognosis.

The results of this study should be interpreted with some caution. First, Type D personality was not assessed at the time of the index event, as described previously [18]. This may have biased our results, as patients who died between 0 and 6 months after PCI did not have the opportunity to fill in the psychological questionnaire. This is, however, likely to have led to an underestimation of the impact of Type D rather than an inflation given

that Type D patients are at increased risk of adverse prognosis. Second, the results may not be generalizable to the total sample given that the response rate was 65% and that responders and non-responders differed on one baseline characteristic (i.e. age). Third, we had no information on left ventricular dysfunction, which is an established risk factor for adverse prognosis. In multi-variable analysis, however, we did control for multivessel disease, an objective measure of disease severity. Finally, we had no information on the use of psychotropic medication, participation in cardiac rehabilitation, and health-related behaviours, except for smoking, which may have influenced the endpoint. Despite these limitations, an advantage of the current study is that the results reflect the 'real world' of interventional cardiology, as the sample consisted of unselected patients. Later analyses of the RESEARCH registry population have shown that 68% of the patients would not have been included in clinical trials owing to their more complex clinical profile [30].

In conclusion, this study showed that Type D personality moderates the effect of PCI on clinical outcome 2 years after the index event despite treatment with the latest innovation in interventional cardiology. This shows that Type D is also a risk factor in the drug-eluting stent era. The inclusion of psychological risk factors in general, and personality factors in particular may optimize risk stratification in clinical practice in the drug-eluting stent era.

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No conflicts of interest exist.

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